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McCUNE-ALBRIGHT SYNDROME

PENELOPE PHILBRICK FEUILLAN, M.D.

In its classic form the McCune-Albright syndrome (MAS) is the triad of polyostotic fibrous dysplasia, café-au-lait pigmentation, and precocious puberty; over 90 percent of these patients are female. A recent study of DNA extracted from affected tissues has revealed evidence for a somatic mutation in an activating component (the $G_s\alpha$ subunit) of the adenylate cyclase signal transduction system, supporting the hypothesis that a defect at the end organ level is the underlying mechanism in MAS. Hopefully, this new finding will lead to the design of more effective therapy for this complex disorder.

The diagnosis of MAS is not always obvious because of its broad spectrum in clinical presentation. The bone disease may be severe and progressive in early infancy, milder cases may manifest later in childhood as unequal limb length or facial asymmetry, and a few children have no signs or symptoms of fibrous dysplasia. In such cases the lesions become apparent only with technetium bone scan. Whereas the café-au-lait pigment typically appears as broad, irregular macules that often terminate abruptly at the ventral midline, it is occasionally confined to small areas in the nuchal region or the cleft of the buttocks. In 10 to 20 percent of patients, no abnormal pigmentation is found.

The precocious puberty in MAS characteristically presents as breast development and vaginal bleeding in a girl under 2 to 3 years of age. Some girls have regular menses and rapid pubertal development, whereas others have intermittent bleeding that may not recur for months or years. In such patients rates of growth and bone

maturation can be normal and puberty occasionally occurs at the normal age. The elevated serum estrogen levels in girls with MAS are related to ovarian cysts, which enlarge and resolve over periods of days to weeks. Serum gonadotropin levels and the gonadotropin responses after luteinizing hormone–releasing hormone (LHRH) are usually suppressed below the normal range. However, early in the course of the disorder or when the ovarian activity is in remission, the gonadotropin levels may be within the normal prepubertal range. Some older patients with bone ages over 11 to 12 years have exhibited pubertal gonadotropin responses, presumably a result of maturation of the hypothalamic regulatory centers following sex steroid exposure.

Additional forms of endocrine dysfunction are seen in many patients with MAS, the most common of which are hyperthyroidism and goiter. Less frequently, patients may exhibit hyperadrenocorticism and Cushing's syndrome. Like the ovarian disease, hyperfunction of the thyroid or the adrenal is associated with suppressed serum levels of the corresponding stimulating factor. Other endocrinopathies include growth hormone hypersecretion and acromegaly. Hyperphosphaturia may result in hypophosphatemia and, occasionally, rickets.

MAS patients appear to be at increased risk for breast cancer (possibly related in part to prolonged estrogen stimulus) and osteogenic sarcoma. Physicians must be prepared to coordinate management of multiple forms of endocrine dysfunction with surgical treatment for fractures and deformities, which can be lasting sequelae of fibrous dysplasia of bone. Unfortunately, no medical treatment has yet been proven to slow the progression of the bone disease.

THERAPY FOR PRECOCIOUS PUBERTY

The decision to initiate therapy for precocious puberty in a girl with MAS is usually based on a history of recurrent menses, rapid pubertal development, and a significant degree of bone age advance (>2 S.D. above the chronologic age). Precocious puberty in most girls with MAS is gonadotropin independent and hence does not respond to treatment with the long-acting LHRH agonist analogs. Our own clinical studies have focused on agents that block estrogen biosynthesis.

Testolactone

Testolactone is a competitive inhibitor of aromatase, the enzyme that converts testosterone and androstenedione to estradiol and estrone. This agent is a derivative of testosterone (a lactone ring is substituted for the D ring of the steroid nucleus). A 6 month pilot study of testolactone in five girls with MAS showed decreases in serum levels of estradiol and estrone, a decrease in the frequency of menses, and a slowing in rates of growth and bone maturation. Ongoing long-term clinical trials of testolactone have demonstrated continued benefit in approximately 70 percent of patients.

Pretreatment Evaluation

Before treatment is started, an LHRH stimulation test is performed to confirm gonadotropin-independent puberty. It is also helpful to measure baseline serum levels of estradiol and estrone and levels of their biosynthetic precursors testosterone and androstenedione. Radiography of the hand and wrist to determine bone age should be done. Pelvic ultrasonography can document the presence and dimensions of ovarian cysts. A convenient method of quantifying the extent of ovarian cyst activity is to measure the mean ovarian volume (MOV):

$$V = \text{length} \times \text{width} \times \text{thickness} \times 0.5$$

$$MOV = V^{\text{right ovary}} + V^{\text{left ovary}} \div 2$$

Pretreatment laboratory studies should include thyroid hormone levels and also tests of renal and hepatic function, because testolactone is metabolized in the liver and excreted in the urine (see later). The pretreatment evaluations are repeated at 6 month intervals during treatment.

Technetium bone scan is the most sensitive method for identifying sites of active bone disease. In patients with extensive bone involvement, short stature in adulthood is a consequence of both early epiphyseal fusion and also of limb deformities, fractures, and scoliosis caused by fibrous dysplasia. In such a patient, an improvement in adult stature achieved by slowing the rate of bone age advance could be offset by the effects of bone disease. Clinical trials have not shown whether treatment of precocious puberty of MAS has an effect on the progression of bone lesions.

Treatment Protocol

Because girls may complain of abdominal pain and diarrhea early in the course of therapy, testolactone is begun at a low dose (10 mg per kilogram per day) and increased over a period of 3 to 4 weeks to the final oral dose of 40 mg per kilogram per day, with divided doses given every 6 hours. If a patient has distress, the dose is reduced for 3 to 4 days. Most patients tolerate therapy well, although the frequent dosing schedule may be difficult to follow.

Patients who respond to treatment exhibit decreased levels of serum estrone and estradiol, decreased frequency of menses, and slowing in rates of growth and bone maturation. Because the natural course of precocious puberty in MAS is often intermittent, therapy should be continued for 6 to 12 months to estimate its effectiveness. In a patient who responds to testolactone, therapy is continued until normal puberty or until a bone age reveals epiphyseal fusion (bone age of 15 to 16 years).

Secondary Central Puberty

A few girls with MAS and bone ages close to the pubertal range (>11 years) exhibit a pubertal pattern of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) responses after LHRH during testolactone treatment, indicating the onset of gonadotropin-dependent puberty. In these patients therapy with one of the long-acting LHRH agonists may be added to the testolactone regimen to suppress pituitary gonadotropin secretion. The depot preparation of leuprolide acetate offers the most convenient approach to treatment. The usual dose is 7.5 mg (300 to 500 μg per kilogram) every 28 days. There is also extensive clinical experience with the potent LHRH agonist analog deslorelin (4 μg per kilogram per day SC) and histrelin (10 μg per kilogram per day); these two agents are expected to be commercially available within a short time.

An LHRH stimulation test is performed at 3 to 6 month intervals after treatment with the LHRH analogs is initiated to confirm that gonadotropin levels are suppressed.

As yet, there are no studies demonstrating the long-term effectiveness of combined therapy with testolactone and the LHRH analogs in girls with precocious puberty due to MAS. Furthermore, the high cost of these and other new drugs (Table 1) together with the need for a prolonged course of treatment, makes their use prohibitively expensive for many families.

Some girls who initially respond well to testolactone exhibit recurrent menses, ovarian cysts, and elevated estrogen levels after 2 to 3 years of therapy. The gonadotropin responses to LHRH in these girls usually remain low or prepubertal, ruling out the onset of secondary central puberty. This apparent escape from control may represent tissue resistance to the effects of testolactone, an increase in metabolism and excretion, or in some cases decreased compliance.

Adverse Effects of Testolactone

In girls with MAS, the only adverse effect attributable to testolactone, other than transient cramping and diarrhea, has been an increase in serum levels of hepatic transaminases (serum glutamic-oxaloacetic transaminase, serum glutamic-pyravate transaminase, and gamma-glutamyl transpeptidase) in one patient with preexisting elevation of these enzymes and biopsy-proven liver disease. The transaminase levels returned to their pretreatment levels upon discontinuation of testolactone, and there was no clinical evidence of deteriorating liver function; however, it is important to confirm normal hepatic function prior to initiation of testolactone treatment.

No MAS patient has developed clinical evidence of androgen excess, and the serum levels of androstenedione and testosterone have remained low or in the pubertal range. The presence of metabolites of testolactone may, however, lead to abnormal urinary 17-ketosteroid and 17-hydroxysteroid measurements.

Newer Drugs

Clinical trials of a potent, nonsteroidal competitive inhibitor of aromatase, fadrozole hydrochloride, are planned for girls with gonadotropin-independent precocious puberty. Because of the lower daily dose and the twice daily dosing schedule, it is hoped that use of this agent will bring about improvement in compliance and more effective suppression of serum estrogen levels.

Nonsteroidal estrogen antagonists such as tamoxifen have not been studied extensively in girls with precocious puberty. The safety of these agents for

Table 1 Commercially Available Agents Used for Endocrine Dysfunction in Patients with MAS

Agent	*Form*	*Cost* (U.S. $)*	*Usual Dosage*
Aromatase Inhibitor			
Testolactone (Teslac)	50 mg tablets	120.00	40 mg/kg/day qid
Antiandrogen			
Spironolactone	25 mg tablets	3.54–7.49	5–6 mg/kg/day bid
(Aldactone)	25 mg tablets	36.00	
Ketoconazole (Nizoral)	200 mg tablets	230.00	600 mg/day tid
Progestin			
Medroxyprogesterone acetate depot (Depo-Provera)	100 mg/ml (5 ml vial)	36.18/vial	50–200 mg monthly
LHRH Analog			
Leuprolide acetate (Lupron Depot)	3.75 mg†	356.00/vial	7.5 mg monthly
	7.50 mg	437.00/vial	
Somatostatin analog			
Octreotide (Sandostatin)	100 μg/ml (1 ml ampule)	367.14/50 ampules	300 μg/day (tid)
1.25–Dihydroxyvitamin D	500 μg/ml (1 ml ampule)	1680.36/50 ampules	
Calcitriol (Rocaltrol)	0.25 μg capsules	97.44	0.5–2.0 μg daily
Thionamide			
Propylthiouracil	50 mg tablets	2.40–7.05	5 mg/kg/day tid-qid

*Wholesale price per 100 tablets/capsules or per vial, as indicated. Data from Montvale, NJ: Medical Economics Data, 1993 Red Book.
†Supplied as lyophylized compound with diluent for injection.

long-term use in pediatric patients has not been established.

Alternative Treatments

Medroxyprogesterone Acetate

Medroxyprogesterone acetate is a progestin that has been used to control menstrual bleeding in girls with precocious puberty and that may be effective for this purpose in girls with MAS who fail to respond to other treatments. The preferred form is the depot preparation, which is administered intramuscularly at a dose of 50 to 200 mg (4 to 15 mg per kilogram) once per month. There are no long-term studies of the efficacy of medroxyprogesterone acetate in the treatment of groups of girls with MAS, however, and no evidence that it can slow the rate of bone maturation. At high doses, it may have glucocorticoid effects, and it has also been linked to the occurrence of tumors in experimental animals.

Surgery

Ovariectomy or ovarian cystectomy should be considered a last resort for treating precocious puberty in MAS, because cysts almost always recur in the remaining ovarian tissue. There is also a potential loss of fertility (some adult women with MAS are able to conceive, and most of these bear normal children), as well as the risks of anesthesia and of scarring and adhesions.

Males with MAS

Precocious puberty due to autonomous testicular hyperfunction, together with the skin, bone, and endocrine manifestations of MAS, is occasionally seen in males. Because pubertal development and rates of linear growth and bone maturation in boys are mediated by both androgens and estrogens, therapy for boys with MAS is directed at both classes of sex steroid. We have used this form of treatment in boys with the gonadotropin-independent familial form of male precocious puberty (FMPP; also termed *testotoxicosis*).

Spironolactone, a blocker of androgen action, is given at a daily dose of 5.7 mg per kilogram. Although no adverse effects have been observed at this dose, patients are monitored carefully for evidence of mineralocorticoid deficiency and electrolyte imbalance and are instructed to discontinue the drug during periods of acute illness.

The aromatase inhibitor testolactone (see earlier) is given in conjunction with spironolactone to block estrogen biosynthesis. This combined therapy has been effective in lowering serum testosterone levels and in controlling the rapid rates of growth and bone maturation in FMPP. In addition, gynecomastia, a common secondary effect of antiandrogen treatment, did not occur in patients receiving both spironolactone and testolactone.

As for girls with MAS, pretreatment evaluations include an LHRH stimulation test, levels of testosterone and estradiol, and tests of hepatic and renal function. Patients are monitored at least every 6 months, including serum electrolyte levels in those taking spironolactone. In boys whose gonadotropin responses after LHRH indicate the advent of secondary central puberty, therapy with one of the LHRH agonists may be added to the regimen.

Alternative antiandrogenic agents include the antifungal agent ketoconazole, which has been used at a daily dose of 600 mg in the treatment of boys with FMPP. Ketoconazole was well tolerated in this group of patients, although it is known to have antiglucocorticoid actions and has been associated with hepatic damage in a small number of subjects.

THYROID ABNORMALITIES

Thyroid abnormalities are found in 30 to 40 percent of patients with MAS; the incidence is reported to be higher in males. Characteristically, serum TSH levels are low or undetectable, thyroid hormone levels are normal or elevated, and structural abnormalities such as hypoechoic or hyperechoic regions (indicative of cysts or nodules) are seen on ultrasonography. In children and young adults the thyroid disorder often takes an indolent course; goiter may remain inapparent or develop gradually, and patients may remain clinically euthyroid for years. No long-term studies have yet revealed what percentage of these patients will eventually require medical intervention.

In the event of symptomatic hyperthyroidism, administration of a thionamide such as propylthiouracil can reduce serum thyroid hormone levels and normalize thyroid-stimulating hormone. The doses used in MAS patients are comparable to those in patients with Graves' disease (3 to 6 mg per kilogram per day in children, 300 to 600 mg per day in adults divided every 6 to 8 hours). The risk of adverse reactions such as agranulocytosis and granulocytopenia appears to be no greater in MAS than in other patients.

Thyroidectomy or hemithyroidectomy has historically been the definitive therapy for hyperthyroidism and goiter in MAS patients. Radioiodine has also been used effectively for thyroid ablation.

GROWTH HORMONE AND ACROMEGALY

Growth hormone (GH) hypersecretion is an uncommon finding in MAS and is usually not identified until patients have reached early or mid-adulthood. In children a rapid rate of linear growth and elevated serum levels of insulin-like growth factor (IGF) I may be attributed to the elevated levels of sex steroids. In many patients, the facial features of acromegaly may be obscured by the skull and facial deformities caused by fibrous dysplasia. The diagnostic criteria are similar to those of non-MAS patients with acromegaly. In affected

subjects, serum IGF-I levels are elevated, growth hormone levels do not fall or may rise paradoxically following an oral glucose load, and there may be stimulation of growth hormones after thyrotropin-releasing hormone.

Octreotide is a long-acting somatostatin analog that has been used successfully to suppress growth hormone secretion in acromegaly, including a small number of adult patients with MAS. The daily dose of octreotide is usually 300 μg given subcutaneously in three divided doses. Side effects of treatment include abdominal pain and nausea in the early weeks of treatment, and a 65 and 20 percent incidence of bile sludge formation and gallstones, respectively.

Bromocriptine has not been useful in suppressing growth hormones in patients with MAS. Pituitary adenomectomy is often impractical as a result of the presence of fibrous dysplasia in the sellar region, and clinicians hesitate to use radiation therapy because of reports of osteogenic sarcoma and other bone neoplasms in MAS patients.

HYPOPHOSPHATEMIA AND RICKETS

Those who care for patients with MAS should keep in mind that the onset of rickets may be obscured by the radiologic and hematologic stigmata of the bone disease. Serum calcium level in MAS patients is typically normal, and serum phosphorus level may be normal or low normal. Serum alkaline phosphatase and urinary hydroxyproline levels range from normal to very elevated because of polyostotic fibrous dysplasia; these laboratory indices do not always correlate with the extent of skeletal involvement, however.

The diagnosis of rickets in MAS is usually based on the classical radiologic stigmata of epiphyseal widening, cupping, and fraying. In some cases serum parathyroid hormone level may also be elevated. Treatment is comparable to that for other forms of hypophosphatemia rickets; vitamin D is usually administered as calcitriol (1,25-hydroxy vitamin D_3) at an initial dose of 0.250 μg given twice daily, together with a phosphorus preparation such as K-Phos (250 mg given four to six times daily). Patients are carefully monitored for hypercalcemia, renal stone formation, and secondary hyperparathyroidism.

HYPERADRENOCORTICISM AND CUSHING'S SYNDROME

Autonomous adrenocortical hyperfunction causing Cushing's syndrome is a rare complication of MAS; most of the reported cases have occurred in infants under 3 months of age. Bilateral adrenalectomy was performed in these patients, followed by mineralocorticoid and glucocorticoid replacement therapy. As yet, there are no reports of successful medical management of Cushing's syndrome in MAS patients, although antiglucocorticoid agents such as ketoconazole and the antiprogestin RU 486 have been used for this purpose in other patients. Our own experience with a girl with MAS who had transient hypercortisolemia and cushingoid appearance in infancy, followed by normal adrenocortical function later in childhood, suggests that some patients can be managed conservatively.

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